doi.org/10.36721/PJPS.2025.38.3.REG.14083.1

# Drug-drug interactions with azithromycin during COVID-19: An evidence of contribution towards patient mortality

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**Abstract**: The study was conducted to evaluate the prevalence of Drug-Drug Interactions (DDIs) of Azithromycin and its impact on patient mortality and microbial resistance during the first wave of COVID-19. The study was performed in tertiary care hospitals located in various areas of Karachi, Pakistan. A cross sectional retrospective study on a sample size of 300 patients was conducted (Jan - Dec 2020) on in-patients receiving Azithromycin as part of their therapeutic regimen. Data was collected using a structured and validated tool. The Medscape Drug Reference database was applied to assess the DDIs. The presence of DDIs was observed in 224 patients (75 %) involving 28 drugs with a total of 346 interactions. Among them, majority (60 %) were severe followed by moderate (33 %) and mild interactions (7 %). Among 300 patients, a total of 41 mortalities was observed with highest percentage (90%) in patients with drugs causing severe interactions i.e. enoxaparin and hydroxychloroquine. The moderate interaction group exhibited 10% mortality involving piperacillin. Additionally, out of 346 interactions, only one due to calcium carbonate was found to affect the bioavailability of azithromycin. Our data reveals the high prevalence of DDIs with Azithromycin during the first wave of COVID-19, which has most likely contributed towards the mortality.

**Keywords**: Azithromycin; Drug-drug Interactions; Mortality; COVID-19.

*Submitted on 06-02-2025 – Revised on 07-04-2025 – Accepted on 12-04-2025*

## INTRODUCTION

There has been a global concern regarding the adverse effects and mortality occurring due to drug interactions. It is estimated that up to 30% of all adverse effects are due to drug-drug interactions (DDI) and hence negatively impact therapeutic outcomes (Soherwardi, Chogtu, and Faizal 2012). A number of techniques have been employed at regional and provincial levels in order to ensure that these interactions are avoided whenever possible. However during COVID-19 due to the general state of panic, a high prevalence of DDIs was reported (Cantudo-Cuenca *et al*. 2021). This was amplified by the absence of standardized treatment options or preventive measures. Treatment options mainly comprised of repurposed drugs that had shown efficacy in other viral diseases. Since, more than 50% of COVID-19 patients suffered from at least one comorbidity (Chen *et al*. 2020), this further enhanced the likelihood of the occurrence of DDIs due to polypharmacy. A study reported that the mortality rate was significantly higher in patients with underlying disease (Team 2020) and in patients who were administered multiple drugs (Iloanusi, Mgbere, and Essien 2021). The large influx of the patients within the hospitals and prophylactic measures being taken for the protection of other hospitalized patients also played a significant role (Cantudo-Cuenca *et al*. 2021).

One of the most commonly used antibiotic in Pakistan during the first wave of COVID-19 was azithromycin (Rosenberg *et al*. 2020). The use of azithromycin was reported to have increased exponentially during this time period (Al-Azzam *et al*. 2021, Ul Mustafa *et al*. 2021). The excessive usage was mainly attributed to the promising experimental trials and its past usage in the treatment of similar viruses (Gautret *et al*. 2020). In the uncertain environment prevailing during that time a number of other medications were also being used without any concrete evidence of efficacy (Manjhi *et al*. 2021). This experimental use of medications in combination with azithromycin led to high rates of DDIs (Cantudo-Cuenca *et al*. 2021). The DDIs associated with azithromycin were mainly due to altered pharmacokinetic properties such as induction or inhibition of cytochrome P450 isoenzymes or their pharmacodynamics properties (Manjhi *et al*. 2021). These in turn lead to adverse effects and suboptimal plasma concentrations. The correlation of DDIs with the development of resistance against antibiotics helps to ensure optimal treatment protocols in treatment of patients. Additionally, the extensive use of azithromycin is also reported to have the ability to increase the resistance rate of other antibiotics (Doan *et al*. 2020).

However, there is a scarcity of studies showing potential DDIs that occurred in patients receiving azithromycin during this period. Keeping this into account, this study was designed to analyze the occurrence of DDIs in patients receiving azithromycin along with other therapies during the first wave of COVID-19. The aim was to evaluate the prevalence of DDIs due to azithromycin and its effect on the mortality and the rate of resistance.

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## MATERIALS AND METHODS

This retrospective cross sectional study was conducted for a period of 12 months in various tertiary care hospitals of Karachi. The data was extracted through in-patients receiving azithromycin as part of therapy. For data collection, a sample size of 300 (n = 292) was calculated per 'Daniel's formula for cross-sectional prevalence studies' with d = 0.025 and P = 0.05 for infinite population (Pourhoseingholi, Vahedi, and Rahimzadeh 2013). The sample population was selected through convenience sampling. Data was collected using a structured and validated Data Extraction Form. This Data Extraction Form was self-generated and validated with the help of two subject experts and a pilot study as explained earlier (Li T 2021). It included demographic profile; admission diagnosis; azithromycin dosage and frequency ordered, dispensed and administered; duration of therapy; concurrent medications being used; and the end result of the therapy. Ethical Approval (reference number: 4060821STPHA) was obtained from ERC, Ziauddin University in August 2021 prior to collection of data.

The Medscape Drug Reference database was used to assess the DDIs (Medscape 2023). This is an interaction calculation tool, which helped to identify possible interactions among the drug therapy in a patient. The result of the analysis includes risk and ratings scales. The database also discusses the mechanism of the interaction. The DDIs were characterized as "Serious" "Moderate" and "Minor" DDIs. They were further characterized as being pharmacokinetic or pharmacodynamics in nature. However, drugs causing an increase in QT interval were characterized separately.

Descriptive statistics was performed using 'Statistical Package for Social Sciences' SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

Of the 300 patients included in the study, 207(69%) were males and 93(31%) were females. There were 162(54%) adults with mean age 40.06±10.48 years, followed by 120(40%) geriatrics with mean age 70.37±6.94 years 18(6%) pediatrics with mean age 13.5±3.60 years.

Out of 300 patients, the presence of DDIs involving Azithromycin was observed in 224 patients (approximately 75%). A total of 346 interactions were noted in aforesaid patients (table 1). Out of which 23 (7%), 114 (33%) and 209 (60%) were found to be mild, moderate and severe respectively. The patient mortality was found to be 4 (10%) and 37 (90%) in moderate and severe interactions respectively.

Out of 28 drugs identified to be interacting with azithromycin, 7 (25%) caused minor interactions, 15 drugs (54%) caused moderate interactions while 6 (21%) caused severe interactions. The details of the drugs and the type of interaction along with their frequency are given in table 2.

It was further observed that three interacting drugs were common to all regimens in which mortality was observed (table 3). Piperacillin shows moderate drug-drug interaction with azithromycin as the effects of piperacillin are increased when the two drugs are administered together. Whereas, hydroxychloroquine and enoxaparin both exhibit severe interactions when administered with azithromycin. Increased effect of enoxaparin is observed whereas hydroxychloroquine tends to increase QTC interval.

Among the 346 interactions, only single involving calcium carbonate was found to decrease the bioavailability of azithromycin and hence may have contributed towards the increase in microbial resistance.

## DISCUSSION

Drug-drug interactions have been a cause of morbidity and mortality globally. During COVID-19, the unprecedented situation demanded quick decisions at physicians end. Keeping this into account, the present study evaluated the prevalence of drug-drug interactions between azithromycin and other drugs along with its potential impact on patient mortality and microbial resistance pattern during the first wave of COVID-19.

Our study showed that almost 75% (n = 224) of patients under study had least at one drug interacting with azithromycin. Although similar trend has been observed world over regarding the number of interactions among the drugs administered during COVID-19 (Conti *et al*. 2022), the figure obtained in present study is alarmingly high. This can most likely be attributed to the fact that this data was collected for the patients hospitalized during the first wave of COVID-19 i.e. January 2020 to December 2020. During this time, there was a generalized state of panic owing to the rapid spread of the virus and the consequent high rate of mortality observed globally. There was also a lack of standardized therapeutic regimen which led to experimental use of repurposed drugs. Several drugs were believed to be effective and were being used simultaneously in hope of producing a positive therapeutic response. All these factors mitigated the importance of the probable interactions and their consequent effects on the outcome.

Our data revealed that there were 346 instances of drug interaction with azithromycin (table 1). The intensity of the interactions are classified as mild, moderate and severe in

lieu with the standard rating system (Medscape 2023). In the present study, majority (60%) of interactions belonged to the class of severe group followed by moderate (33%) and mild (7%). It is worth noting that the severity of interaction positively co-related with the mortality of patients. COVID-19 was marked by high mortality rate (Adamiszak *et al*. 2022). However, in line with our findings, studies have highlighted the possibilities that some of the aggravation of the disease could have been possibly due to drug-drug interactions (Hodge *et al*. 2020). The further excavation of data identified 28 drugs that interacted with azithromycin (table 2). Among them, 6 drugs (enoxaparin, hydroxychloroquine, ondansetron, heparin, albuterol and escitalopram) were responsible for severe interactions. The enoxaparin and hydroxychloroquine (HCQ) constituted the major burden of severe interactions i.e. 68% and 20% respectively. The former was received by patients as part of their regular regimen. It is an anticoagulant medication used to treat and prevent deep vein thrombosis (DVT) and pulmonary embolism (PE). It is also used in those with acute coronary syndrome (ACS) and heart attacks. It was the preferred first line anticoagulant for patients diagnosed with COVID-19 (Barnes *et al*. 2020). According to available data however when it is co administered with azithromycin a severe interaction is produced. Azithromycin increases effects of enoxaparin by decreasing metabolism leading to enhanced bioavailability and ultimately bleeding (Medscape 2023). It is worth noting that hemorrhage has been reported as a frequent cause of mortality in COVID-19 patients (Dorgalaleh 2020) and was associated with administration of anticoagulants and was found to be population sensitive (Thomas and Scully 2022). However, the underlying cause of such bleeding was not known. Our data highlights that the DDI between azithromycin and enoxaparin most likely underlie aforementioned outcomes. On the other hand, hydroxychloroquine is primarily used to prevent and treat malaria in areas where malaria remains sensitive to chloroquine. Initially, it was believed that its combination with azithromycin in COVID-19 may produce positive therapeutic outcomes. A number of trials supported this claim but by the end of year 2020 the RECOVERY trial established this to be untrue (Ayerbe *et al*. 2022). However, before the completion of this trial the combination of HCQ and azithromycin was used widely. They both tend to increase the QTC interval (Medscape 2023). Studies have shown that patients who are concurrently administered azithromycin and HCQ have a greater chance of QT prolongation when compared with the control group (Kim *et al*. 2020). This was mainly attributed to the additive cardio toxic side effects already reported in both drugs and the increased levels of HCQ due the CYP3A4 inhibition by azithromycin (Zequn *et al*. 2021). It is worth noting that out of 41 mortalities observed in our study, almost 61% was attributed to cardiopulmonary arrest. This further advocates that the high mortality observed during first wave of COVID-19 was also exacerbated by DDIs such as that of azithromycin and HCQ. It is observed in our study that both of these drugs led to the interactions leading to mortality (table 3). Although literature review does not show any evidence of mortality due to these interactions, our data and that of drug interaction points towards the probability that this could have been an underlying contributing factor in aggravation and death of the patient. The frequency of these drugs within the patients who died is an alarming indication and one that requires further studies. Furthermore, in case of moderate interactions, the predominant (58%) drug was Piperacillin. It is a broad-spectrum β-lactam antibiotic used most commonly in combination with tazobactam for treatment of serious hospital acquired infections. During COVID-19 initially its consumption was increased due to unclear therapeutic guidelines. Azithromycin when co administered with piperacillin, decreases effects of piperacillin by pharmacodynamics antagonism (Medscape 2023). It is considered a moderate interaction and requires dose management or monitoring of therapy. The science of drug-drug interaction is still unclear. Although literature provides us with all known possible interactions, it fails to take into account the various confounding variables surrounding real life practice. The exact implications of these interactions are hence difficult to interpret especially in a retrospective study. However, based on the provided literature, we have interpreted our data and consider it a probable or a contributing factor in the mortality seen among patients in whom interactions were identified.

Azithromycin consumption was significantly high during the first wave owing to the number of trials and theories supporting its efficacy in the treatment either alone or in combination with HCQ. Another reason for its wide spread (Al-Azzam *et al*. 2021, Ul Mustafa *et al*. 2021), use was its established efficacy in the prophylaxis and treatment of respiratory diseases specially pneumonia. Within Pakistan, the burden of use was further increased when typhoid epidemic started. The presence of XDR strain further propagated the use of azithromycin. This increased consumption in turn led to a significant increase in its rate of resistance (Kournoutou and Dinos 2022). One of the objectives of conducting this study was to determine if the interactions in anyway had contributed to this increase in resistance. It was observed that in spite of staggering prevalence of interactions only a single interaction involving calcium carbonate can enhance chances of microbial resistance towards azithromycin. Upon co-administration of calcium carbonate with azithromycin, the change in the stomach pH by former lowers the absorption of azithromycin. This in turn increase the chances of microbial resistance due to decreased bioavailability (Medscape 2023). However, since there is only one such incidence and there are no other interactions which could have contributed towards resistance, we have concluded that the presence of interactions did not contribute towards the increase in resistance pattern noted following COVID-19 era.

**Table 1**: Type and Frequency of DDIs with Mortality Rates

| Drug-Drug Interactions | | Mortality |
|---|---|---|
| Type | Frequency (%) | Frequency (%) |
| Mild | 23 (7) | 0 (0) |
| Moderate | 114 (33) | 4 (10) |
| Severe | 209 (60) | 37 (90) |
| Total | 346 (100) | 41 (100) |

**Table 2**: Drugs Interacting with Azithromycin: Their Effects and Frequency

| S. No. | Type of Interaction | Drug | Effect of Interaction | N |
|---|---|---|---|---|
| 1 | Mild | Amoxicillin | Decrease effect of Amoxicillin | 6 |
| 2 | | Sulfamethoxazole | QTC increase | 5 |
| 3 | | Trimethoprim | QTC increase | 5 |
| 4 | | Paroxetine | QTC increase | 2 |
| 5 | | Levofloxacin | QTC increase | 2 |
| 6 | | Voriconazole | QTC increase | 2 |
| 7 | Moderate | Ampicillin | Decrease effect of Ampicillin | 1 |
| 8 | | Piperacillin | Decrease effects of Piperacillin | 66 |
| 9 | | Atorvastatin | Increase level of Atorvastatin | 16 |
| 10 | | Quetiapine | QTC increase | 6 |
| 11 | | Artemether | QTC increase | 5 |
| 12 | | Ciprofloxacin | QTC increase | 4 |
| 13 | | Formoterol | QTC increase | 4 |
| 14 | | Citalopram | QTC increase | 3 |
| 15 | | Amitriptyline | QTC increase | 2 |
| 16 | | Clarithromycin | QTC increase | 2 |
| 17 | | Indapamide | QTC increase | 1 |
| 18 | | Trazodone | QTC increase | 1 |
| 19 | Severe | Calcium Carbonate | Decrease level of Azithromycin | 1 |
| 20 | | Rivaroxaban | Increase level of Rivaroxaban | 1 |
| 21 | | Cefpodoxime | Decrease effects of Cefpodoxime | 1 |
| 22 | | Cetirizine | Increase levels of Cetirizine | 1 |
| 23 | | Enoxaparin | Increase effect of Enoxaparin | 142 |
| 24 | | Hydroxychloroquine | QTC increase | 42 |
| 25 | | Ondansetron | QTC increase | 22 |
| 26 | | Heparin | Increase effect of Heparin | 1 |
| 27 | | Albuterol | QTC increase | 1 |
| 28 | | Escitalopram | QTC increase | 1 |

**Table 3**: DDIs Leading to Mortality

| Type of Interaction | Drug | Effect of Interaction |
|---|---|---|
| Moderate | Piperacillin | Increase the effect of Piperacillin |
| Severe | Enoxaparin | Increase effect of Enoxaparin |
| | Hydroxychloroquine | QTC increase |

## CONCLUSION

Our study shows a high prevalence of DDIs with Azithromycin during the first wave of COVID-19. It is apparent that these DDIs did not contribute in the microbial resistance rate towards Azithromycin. However, our data advocates that the DDIs has most likely contributed to the high mortality observed during first wave of COVID-19.

***Conflicts of interest***

The authors declare no conflicts of interest.

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